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Comparison of various betamimetics on preterm labor, survival and development of the child

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1 Introduction

Prolonged treatment with β-sympathomimetics for inhibition of premature labor has been accepted worldwide for a couple of years. The initial use of drugs like isoxyprimchloride with a mixed β_1 and β_2 effect has gradually been exchanged by more selective β_2 stimulatory compounds like ritodrine, salbutamol and terbutaline since both experimental and clinical results have demonstrated their superiority in this context. So far interest has mainly been focused upon 1) the prolongation of pregnancy that can be obtained [7, 11] 2) metabolic influences on the mother and fetus [1, 2] and 3) acute influence on fetal heart rate [3].
In a recent study by FREYSZ *et al.* [4] a long-term evaluation of infants who received β-sympathomimetic drugs while in utero was reported in a case material of 42 children. **In the present study the efficacy of three various β-sympathomimetic drugs on premature labor was compared and the children followed up to 18 months after delivery.**

2 Material and methods

The material includes patients with premature labor attending the Department of Obstetrics and Gynaecology, Sahlgren's University Hospital between August 73 to January 76. Selections of patients were made according to the following criteria:

a) length of gestation 25 to 35 weeks
b) uterine contractions with a frequency of at least 10 per h, registered by use of a cardiotocograph (CTG)
c) cervix not dilated to more than 4 cm
d) no obvious signs of ruptured membranes

According to these criteria 79 of a total number of 152 with preterm labor were included in this study. The patients were divided into three groups treated with either isoxyprine, ritodrine or terbutaline. The choice of treatment for each patient was unselected.
Careful anamnestic obstetric recordings were made with special reference to earlier premature labor and abortions (see Results). All patients were supervised for minimum 24 h in the delivery ward, after which time they were hospitalized for various periods of time depending upon the outcome of treatment. CTG registration was as a rule performed continously during the initial treatment followed by daily registrations for 30 minutes.
At delivery APGAR score was registered after one and five minutes. All children with birth-weights below 2 500 g and/or a reduced APGAR score at 5 minutes (< 7) were supervised and treated in a well-equipped neonatal unit. A special follow-up programme was performed on these children by

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one of the authors, 5, 10 and 18 months after delivery.

2.1 Schedules of treatment

1: Isoxyprine (Duvadilan® FERROSAN Ltd, Sweden). Intravenous infusion: 90 mg isoxypyrine to 1 000 ml Invertos (ACO, Ltd, Sweden). Infusion rate 0.05–0.20 mg/min. After interruption of premature labour as judged from the CTG registration for 15–48 h, treatment with tablets (10 mg × 4–8 daily) was continued for varying periods of time, not exceeding the 35th week of gestation.
2: Ritodrine (PHILIPS-DUPHAR, Netherlands). Intravenous infusion: 100 mg Ritodrine to 500 ml 5.5 % glucose. Infusion rate 100–400 μg/min for 12 to 48 h. After interruption of premature labour treatment with tablets (10 mg × 4–8) was continued in a similar way as for isoxyprine.
3: Terbutaline (Bricanyl®, DRACO, Sweden). Intravenous infusion: 5 mg terbutaline to 1 000 ml 5.5 % glucose. Infusion rate 2.5–15 μg/min for 15 to 48 h. After interruption of premature labour treatment was continued by oral administration of terbutaline (5 mg × 3).
After delivery each child was scored according to APGAR, and when indicated (low birth weight or APGAR < 7 at 5 min) transferred to the intensive neonatal unit. Between 4 to 7 days after delivery each newborn was carefully checked by a pediatrician. The children were thereafter scheduled for a special check up at 5, 10 and 18 months. The aim of the rigorous pediatric follow-up was primarily to reveal intrauterine growth development, perinatal asphyctic syndrome, neonatal respiratory distress (RDS) and mortality. Secondly post-partum growth and psychomotoric development were evaluated.

3 Results

Tab. I summarizes data concerning maternal age, earlier pregnancies, spontaneous abortions and premature delivery, and the gestational age when premature labour started. The groups did not differ significantly in these parameters.
The mean gain in weeks for the three β-mimetics was for Isoxyprine 2.48, Ritodrine 4.45 and for Bricanyl 5.00. If the material for the respective groups is divided in failures (prolongation less than 7 days) and successful cases (prolongation ⩾ 7 days) **a tendency towards a higher success rate with terbutaline compared to the two others was found** (Tab. II).
The choice of method for delivery and the condition of the newborn children as judged from birth-weights, APGAR scores and the presence of respiratory disturbances for the various groups are summarized in Tab. III. An evaluation concerning the weight as related to gestational age was performed comparing actual birth-weight with the expected weight at delivery. No statistical deviation

Tab. I. Obstetrical data of the total number of patients treated for premature labour.

Group	Number of patients	Age of patient	Multigravidae (number of patients)	Earlier spontaneous abortions or premature labour	Start of treatment
Isoxuprine	25	25.5 ± 0.7	15	17	weeks 26–30 n = 8 weeks 31–35 n = 17 mean 31.96 ± 0.80
Ritodrine	29	25.1 ± 0.7	12	15	weeks 26–29 n = 7 weeks 31–35 n = 22 mean 31.62 ± 0.60
Terbutaline	25	26.9 ± 1.7	8	13	weeks 26–30 n = 14 weeks 31–35 n = 11 mean 30.16 ± 0.67

Tab. II. Induced prolongation of pregnancy after treatment with three β-mimetics.

	Isoxyprine		Ritodrine		Terbutaline	
Gain in days from start of therapy to delivery	< 7 days	≥ 7 days	< 7 days	≥ 7 days	< 7 days	≥ 7 days
No of patients	13	12	12	17	9	16
Mean prolongation between start of treatment and delivery (days)	2	40	2	61	2	52
Mean prolongation for each group (days)	17.4 ± 6.2		31.2 ± 5.6		35.0 ± 5.3	
Neonatal age in weeks at delivery	31	37	31	40	30	37

Tab. III. Methods of delivery. Apgar scores and lung complications during neonatal life.

	Isoxyprine		Ritodrine		Terbutaline	
Gain in days from start of therapy to delivery	< 7 days	≥ 7 days	< 7 days	≥ 7 days	< 7 days	≥ 7 days
Normal vaginal delivery	11	12	11	12	8	13
Vacuum extraction	0	0	1	2	1	1
Caesarian section	3	0	–	3	–	2
Mean birth weight (g)	1830	2780	1650	3260	1510	2780
No of children with APGAR < 7 1′	5	2	9	0	4	3
No of children with APGAR < 7 5′	–	–	–	–	–	–
Respiratory disturbances	9	3	9	1	5	2
X-ray verification of preliminary lung complications	4	–	6	–	3	2

was, however, found although 5 children in the total material were smaller than 2 SD from the mean.

At 18 months of age the mean weights of the surviving children in the various groups did not differ from the normal weight at this age. Tab. IV illustrates the mortality in the various groups up to 1 year of age.

There is a considerably high mortality rate in the "failure groups". There is, however, no statistical difference between any of the groups in this respect.

Two children, one in the isoxyprine and one in the terbutaline successful groups, died 4 and 11 months post partum. In both these cases neither autopsy nor bacterial cultures could diagnose the reasons for this outcome. Among the surviving children (Tab. V) two had signs of psychomotoric disturbances at 18 months of age, both belonging to the ritodrine failure group. One child was born after 46 h of ritodrine treatment in gestational week 32 demonstrating both intra- and extrauterine hypoxia signs, complicated by an intracranial haemorrhage

Tab. IV. Mortality rates during the first year of life after treatment of mothers with β-mimetics.

	Isoxyprine		Ritodrine		Terbutaline	
	< 7 days	≥ 7 days	< 7 days	≥ 7 days	< 7 days	≥ 7 days
Total number of delivered children	14*	12	13*	17	9	16
Neonatal mortality (number)	4*	–	4**	–	2	–
Mortality between 7 days and 1 year (number)	2	1	–	–	1	1

*) One pair of twins
**) One stillborn

and a prolonged period of hyperbilirubinaemia (Tab. V). The other child, born in week 28, developed a severe RDS and later on had signs of intracranial haemorrhage.
In neither of the groups a retarded growth rate was found at 18 months of age (Tab. V).

4 Discussion

In the present study three different β-mimetics were compared primarily with reference to their efficacy to prolong pregnancy (see Tab. II). **The more selective β_2-sympathomimetics ritodrine and terbutaline showed almost identical results while isoxuprine turned out to be less potent.** The failure rate in the three various groups were, however, very similar indicating that our criteria for selection of patients includes a comparatively large group which is beyond possibilities for therapy. No placebo group was included in this study mainly due to ethical reasons but in a study by INGEMARSSON [5] 15 patients on terbutaline were compared to a double-blind placebo controlled group in the 28–36 weeks of gestation. In the terbutaline-treated group premature labour was arrested in 80 % of the patients while the corresponding value for the control group was 20 %. It must, however, be pointed out that the majority of cases in INGEMARSSON's study were treated in a later stage of pregnancy than in our study. **Side-effects like tachycardia, tremor and vomiting in the present study were comparable in the three groups** when the different agents were administered as described under Materials and Methods. In INGEMARSSON's study [5] all children survived while the present study demonstrates a high mortality (18.5 %) especially in the isoxyprine group (see Tab. IV). In a recently published multicentre study from the United States [6] the neonatal mortality after ritodrine treatment was 5 %. **The mortality in the present study is divided into neonatal mortality (12.4 %) and mortality within the**

Tab. V. Pediatric follow-up of children to mothers treated with β-mimetics.

	Isoxyprine		Ritodrine		Terbutaline	
Gain in days from start of treatment to delivery	< 7 days	≥ 7 days	< 7 days	≥ 7 days	< 7 days	≥ days
Number of surviving children	8	11	9	17	6	15
Abnormal psychomotoric development (number)	1*	–	2	–	–	–
Mean weight (kg)	11.4	11.6	12.0	11.8	11.3	11.7

*) One child with a moderate hearing defect

first year of life (6.1%). Of importance to point out, though, is the fact that the children included in the group "neonatal mortality" in the present material were all very premature at delivery (mean gestational age 28 weeks and mean body weight 990 ± 71 g, see Tab. I). However, this points to the importance of following the children of mothers who have been treated with β-mimetics beyond the neonatal period. In the present material 5 children out of 15 died much beyond the neonatal period and in two of these cases no obvious reasons for death were found.

It would have been of interest to compare the mortality in a matched untreated control group. However, since the incidence of earlier spontaneous abortions and earlier preterm labor in the case material of this study is approximately 50 % it is already a selected material which cannot be compared to unselected groups of women who deliver preterm.

Low APGAR scores and respiratory disturbances were frequent in all three "failure" groups and showed no significant differences (Tab. III). These findings agree well with the expected incidence of disturbances at this age of gestation and do not seem to be influenced by β-sympathomimetic drugs. In the "success" groups APGAR scores and birth weights do not differ significantly from normal deliveries in the corresponding weeks of gestation. The possible long-term effects on children born by mothers who had been treated with β-sympathomimetic drugs were also investigated by repeated examinations of the children up to 18 months. No significant differences in body weights compared to corresponding controls were found. In 2 cases belonging to the ritodrine "failure" group severe hemiparesis remained at 18 months of age. The first case was born in the 28th week of gestation after 36 h of iv ritodrine treatment. Immediately upon birth both a marked RDS and an intracranial haemorrhage were diagnosed. In the second case born in week 33 with a duration of ritodrine treatment of 48 h both intra- and extrauterine hypoxia were registered. The neonatal period was later complicated by hyperbilirubinaemia and intracranial haemorrhage. **The long-term evaluation thus includes two children with severe cerebral paresis and additional 5 children dying beyond the neonatal period, two of them in unsuspected sudden death. This points to the need of extended supervision of this group of high risk patients** a fact which has also recently been pointed out in a similar study performed by FREYZ et al [4]. In conclusion or data are in accordance with numerous other reports demonstrating that β-sympathomimetics are able to prevent preterm labor and that the more selective β_2 drugs are the most potent in this respect. It must, however, be strongly pointed out that **the possible negative long-term effects on children of treated mothers are still unknown** and the present material cannot exclude such risks. As early as in 1959 RONA et al [8] reported that application to rats of isoproteronol caused "infarct-like lesions" in the myocard. WEIDINGER et al [10] recently reported that fenoterol added to human fetal heart muscle in culture caused degeneration that could be counteracted by addition of the calcium antagonist verapanil. No convincing signs of myocardial necrosis were, however, found in the two cases of sudden death in the present material. Further studies are, however, urgently needed specially focused upon the possible long-term effects on the heart muscle of diseased children.

Summary

During the past five years inhibition of preterm labor by use of β-sympathomimetics has been common practice. The initial use of compounds with mixed β_1 and β_2 effect has gradually been replaced by more selective β_2 compounds. Hitherto the interest has been mainly focused upon the elicited prolongation of pregnancy, possible fetal or maternal metabolic disturbances and the acute influence on fetal heart rate. Only few reports mention the possibility of long-term effects in children of treated mothers.

In the present study the efficacy of three different β-sympathomimetics on premature labour was studied and the children followed for 18 months after delivery.

Seventy-nine patients were treated with either isoxyprine (n = 25), ritodrine (n = 29) or terbutaline (n = 25).

Following criteria were demanded for entering the study: 1) length of gestation 25 or 35 weeks, 2) uterine contractions of at least 10 per hour (CTG registered), 3) cervix not dilated more than 4 cm and 4) no rupture of the membranes. In each group the patients were treated primarily with an intravenous infusion followed by oral administration of the respective compound. The treatment was considered successful if prolongation of pregnancy exceeded 7 days. The "failure" group (pregnancy prolongation < 7 days) was somewhat smaller in the terbutaline group compared to both the isoxyprine and the ritodrine groups.

The prolongation of pregnancy was shorter for isoxuprine ($\bar{x}$ 17.4 days) compared to ritodrine ($\bar{x}$ 31.2 days) and terbutaline ($\bar{x}$ 35.0 days). The children were carefully supervised by pediatricians during the first week of life and thereafter scheduled for a special check up at 5, 10 and 18 months after delivery.

A tendency towards a higher degree of "light for gestational age" in all three groups were found, but this was not statistically significant. At 18 months of age the surviving children did not differ significantly from the normal weight at this age, thus **no retarded growth rate at 18 months of age was found.** Ten children (12 %) died during the neonatal period, while 5 children (6 %) died beyond the neonatal period, two of them unexpectedly and suddenly.

Two children had signs of psychomotoric disturbances at 18 months of age, both belonging to the group treated with ritodrine. The present study confirms earlier reports demonstrating that more selective β_2 compounds are most potent in inhibiting premature labour. **From the long-term evaluation of children of treated mothers a remarkably high incidence of complications occurred (7.8 %).** In this connection it is worth-while to keep in mind the findings of myocardial necrosis reported after isoproteronol treatment to rats and the reports concerning in vitro degeneration in human fetal heart after fenoterol treatment.

It may thus be concluded that treatment with β-sympathomimetics should be restricted to carefully selected groups since **long-term adverse effects on children of treated mothers at present cannot be excluded.**

Keywords: β-sympathomimetics, long term effects fetus: mortality-morbidity, premature labour.

Zusammenfassung

Die Beeinflussung der drohenden Frühgeburt, der Überlebensrate und der kindlichen Entwicklung durch Betamimetika

Seit etwa 5 Jahren werden β-Sympathoathomimetika zur Abwendung einer vorzeitigen Geburt in großem Maße eingesetzt. Die anfänglich verwendeten Verbindungen mit Wirkung auf β_1- und β_2-Rezeptoren wurden nach und nach durch Sypmathomimetika mit selektivem β_2-Effekt ersetzt. Bisher richtete sich das Interesse in erster Linie darauf, wie lange der Geburtszeitpunkt tatsächlich hinausgeschoben werden konnte und ob fetale oder mütterliche Stoffwechselstörungen als Folgen der Behandlung auftraten. Auch die akute Beeinflussung der fetalen Herzfrequenz wurde intensiv beobachtet. Die Möglichkeit eines Langzeiteffektes auf Kinder von behandelten Müttern wurde bislang jedoch nur in wenigen Studien diskutiert.

Die vorliegende Arbeit untersucht die Wirksamkeit von 3 verschiedenen β-Sympathomimetika hinsichtlich einer Schwangerschaftsverlängerung bei drohender Frühgeburt sowie die kindliche Entwicklung während der ersten 18 Monate.

Insgesamt wurden 79 Patientinnen entweder mit Isoxyprin (n=25) oder mit Ritodrin (n=29) oder mit Terbutalin (n=25) behandelt. Es mußten folgende Kriterien erfüllt sein:

1) Dauer der Schwangerschaft entweder 25 oder 35 Wochen
2) mindestents 10 Kontraktionen pro Stunde (nach CTG-Aufzeichnung)
3) Muttermund nicht mehr als 4 cm geöffnet
4) kein Blasensprung

In jeder Gruppe wurde den Patientinnen anfangs die entsprechende Verbindung i.v. infundiert, anschließend oral verabreicht. Die Behandlung galt als erfolgreich, wenn die Schwangerschaft um mindestens 7 Tage verlängert werden konnte. Wir stellten fest, daß in der Terbutalin-Gruppe der Anteil der 'erfolglos' Behandelten (d.h. Schwangerschaftsverlängerung < 7 Tage) verglichen mit den beiden anderen Gruppen am geringsten war.

Mit Isoxyprin wurde im Mittel der geringste Behandlungserfolg erreicht (x=17 4 Tage), gefolgt von Ritodrin (x= 31.2 Tage) und Terbutalin (x=35.0 Tage). Während der ersten 7 Lebenstage wurden die Kinder von Pädiatern sorgfältig beobachtet, und im Alter von 5, 10 und 18 Monaten wurden sie einer speziellen Nachuntersuchung unterzogen.

Wir stellten in allen 3 Gruppen die Tendenz fest, daß die Kinder bei der Geburt für das entsprechende Schwangerschaftsalter zu wenig Gewicht hatten, konnten die Unterschiede aber nicht statistisch sichern. Mit 18 Monaten hatten die Kinder ein altersentsprechendes Gewicht und zeigten damit ein normales Wachstum. Zehn Kinder (12 %) starben in der Neonatalperiode; 5 starben erst nach der neonatalen Phase, wovon bei zweien der Tod unerwartet und plötzlich einsetzte. Bei 2 Kindern beobachtete man im Alter von 18 Monaten psychomotorische Störungen; beide Kinder kamen aus der Ritodrin-behandelten Gruppe.

Die vorliegende Studie bestätigt die Ergebnisse früherer Arbeiten dahingehend, daß Verbindungen mit einem stärkeren β_2-Effekt den Geburtszeitpunkt länger hinauszögern und damit wirksamer sind. **Auf der anderen Seite jedoch ergab die Langzeit-Untersuchung der Kinder eine bemerkenswert hohe Komplikationsrate (7–8 %).** In diesem Zusammenhang möchten wir an tierexperimentelle Untersuchungen erinnern, in denen nach Isoproteronol-Behandlung bei Ratten myokardiale Nekrosen nachgewiesen werden konnten. Darüberhinaus gibt es Arbeiten, die in vitro beobachtete Degenerationsprozesse am menschlichen fetalen Herzen nach Fenoterol-Behand-

lung beschreiben. Unsere Schlußfolgerung lautet daher: die Behandlung mit β-Sympathomimetika sollte ausschließlich auf sorgfältig ausgewählte Patientengruppen beschränkt werden, weil nachteilige Langzeiteffekte bei Kindern behandelter Mütter gegenwärtig nicht ausgeschlossen werden können.

Schlüsselwörter: β-Sympathomimetika, Frühgeburt, Langzeiteffekte: Mortalität, Morbidität.

Résumé

Comparaison des divers bétamimétiques sur le travail prématuré, la survie et le dévéloppement de l'enfant

L'inhibition du travail prématuré par les β-sympathomimétiques ont été d'un usage courant ces 5 dernières années. L'emploi initial de composés avec effet combiné de β_1 et β_2 a fait progressivement place à l'application plus différenciée des composés β_2. Jusqu'ici l'intérêt s'est surtout concentré sur la prolongation explicite de la grossesse, les troubles métaboliques foetaux ou maternels possibles et l'influence marquée sur la fréquence cardiaque foetale. Seuls quelques rapports mentionnent l'éventualité d'effets à long terme chez les enfants de mères ayant subi le traitement.

L'article présent porte sur l'étude de l'efficacité de trois β-sympathomimétiques sur le travail prématuré et l observation des enfants pendant les 18 mois suivant l'accouchement' 79 patients ont été traités soit à l.isoxyprine (n = 25), à la ritodrine (n = 29) ou à la terbutaline (n = 25).

Les conditions requises pour faire l'objet de l'étude ont été: 1) Une durée de gestation de 25 à 35 semaines, 2) des contractions utérines de 10 au moins par heure (CTG enregistré), 3) une dilatation du col de l'utérus ne dépassant pas 4 cm et 4) aucune rupture des membranes. Dans chaque groupe, les patientes ont reçu en premier une infusion intraveineuse suivie de l'administration du composé respectif. Le traitement a été considéré comme réussi lorsque la prolongation de la grossesse a dépassé 7 jours. Le groupe d'«échec» (prolongation de la grossesse < 7 jours) a été un peu plus réduit dans le groupe soigné à la terbutaline que chez les deux autres groupes soignés à l'isoxyprine et à la ritodrine.

La prolongation de la grossesse a été plus courte dans les cas d'isoxyprine (x̄ 17,4 jours) que dans ceux de ritodrine (x̄ 31,2 jours) ou de terbutaline (x̄ 35,0 jours). Les enfants ont été suivis attentivement par les pédiâtres durant la première semaine, puis examinés à 5, 10 et 18 mois après l'accouchement.

On a pu observer dans les 3 groupes une tendance vers un degré plus élevé de ¿light for gestational age¡, mais sans signification statistique. A 18 mois, on n'a relevé aucune différence significative de poids entre les enfants normaux et ceux ayant survécu et, par conséquent, aucun taux de croissance retardée. Dix enfants (12 %) sont morts durant la période néonatale, 5 (6 %) au-delà de cette période dont 2 d'une mort subite et inattendue.

Deux enfants ont manifesté des troubles psychomoteurs à l'âge de 18 mois, tous 2 appartenant au groupe soigné à la ritodrine. L'étude présente confirme les rapports antérieurs ayant démontré que les composés β_2 plus sélectifs sont davantage capables d'inhiber le travail prématureé. **Une évaluation à long terme des enfants de mères traitées a montré une incidence remarquablement élevée de complications (7.8%).** Cette observation incite à porter son attention sur les résultats de nécrose myocardiale enregistrée à la suite d'un traitement à l'isoproteronol sur les rats, et sur les rapports concernant la dégénérescence in vitro du coeur foetal humain après un traitement au fenoterol.

En conclusion, on peut conseiller de restreindre le traitement aux β-sympathomimétiques à des groupes soigneusement sélectionnés, étant donné **l'impossibilité actuelle d'exclure absolument des effets négatifs à long terme sur les enfants de mères ayant subi ce traitement.**

Mots-clés: β-sympathomimétiques, effets à long terme sur le foetus: mortalité-morbidité, travail prématuré.

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